Pergamon

European Journal of Cancer, Vol. 34, No. 7, pp. 1030–1035, 1998

Printed in Great Britain
0959-8049/98 $19.00+0.00

PII: S0959-8049(97)10173-3

Original Paper

Five Days of Oral Topotecan (Hycamtin®), a Phase I and Pharmacological Study in Adult Patients with Solid Tumours

C.J.H. Gerrits,[1] H. Burris,[2] J.H.M. Schellens,[1] A.S.T. Planting,[1] M.E.L. van den Burg,[1] G.I. Rodriguez,[2] V. van Beurden,[1] W.J. Loos,[1] I. Hudson,[3] S. Fields,[3] J. Verweij[1] and D.D. von Hoff[2]

[1]Department of Medical Oncology, Rotterdam Cancer Institute (Daniel den Hoed Kliniek) and University Hospital Rotterdam, Groene Hilledijk 301, 3075 EA, The Netherlands; [2]Cancer Therapy and Research Center and the University of Texas Health Center at San Antonio, Texas, U.S.A.; and [3]SmithKline Beecham Pharmaceuticals, U.K. and U.S.A.

Topotecan is a specific inhibitor of topoisomerase I. An oral formulation of topotecan is available with a bioavailability of 32–44% in humans. A phase I and pharmacological study of the oral formulation of topotecan administered daily for 5 days every 21 days was performed in adult patients with solid tumours to determine the maximum tolerated dose (MTD). Adult patients with a WHO performance status ≤ 2 adequate haematological, hepatic and renal functions, with malignant solid tumours refractory to standard forms were entered into the study. Pharmacokinetics were performed on days 1 and 4 of the first course using a validated high performance liquid chromatographic assay. 29 patients entered the study, all patients were evaluable for toxicity and response. The doses studied in the 29 patients were 1.2, 1.8, 2.3, 2.7 mg/m^2/day and a fixed dose of 4 mg/day without surface area adjustment. A total of 109 courses were given. Dose limiting toxicity (DLT) was reached at a dose of 2.7 mg/m^2/day and consisted of CTC (NCI-Common Toxicity Criteria) grade IV granulocytopenia. The regimen was well tolerated. Non-haematological toxicities were mild, including fatigue, anorexia, nausea, vomiting and diarrhoea. A significant correlation was observed between the percentage decrease in white blood cells versus the area under the curve (AUC(t)) of topotecan lactone ($R = 0.76$ $P < 0.01$) which was modelled by a sigmoidal E_{max} function. The correlation coefficient between the absolute topotecan dose administered and the AUC(t) was $R = 0.52$ ($P = 0.04$). Pharmacokinetics of the fixed dose of 4 mg/day were comparable to the 2.3 mg/m^2/day dose. DLT in this phase I study of five daily doses of oral topotecan every 21 days was granulocytopenia. The recommended dose for phase II studies is 2.3 mg/m^2/day or alternatively, a fixed dose of 4 mg/day.

Key words: topotecan, topoisomerase I, phase I, pharmacokinetics
Eur J Cancer, Vol. 34, No. 7, pp. 1030–1035, 1998

INTRODUCTION

TOPOTECAN, 9-dimethylaminomethyl-10-hydroxycamptothecin, is a water soluble semisynthetic analogue of camptothecin [1]. Like camptothecin, topotecan is a specific inhibitor of topoisomerase I. Topoisomerase I is a nuclear enzyme that resolves topological problems of torsionally strained (supercoiled) DNA. This is achieved by forming a covalent adduct between topoisomerase I and DNA, termed the cleavable complex. This catalytic intermediate creates single strand breaks, allowing the DNA molecule to rotate around the intact DNA strand at the cleavage site, leading to a relaxation of the DNA molecule and in this way replication, transcription and other DNA functions can proceed. These enzyme-bridged breaks are then resealed by topoisomerase I [2–6].

Topoisomerase I inhibitors interfere with the breakage–reunion process by stabilising the cleavable complexes, thereby preventing the resealing of single strand DNA breaks

Correspondence to J. Verweij.
Received 25 Jul. 1997; revised 26 Nov. 1997; accepted 19 Dec. 1997.

in the presence of the drug. Cytotoxicity is more specific to the S phase of the cell cycle in which double strand breaks occur due to prolonged stabilisation of the cleavable complexes [7, 8]. Phase I studies with single daily intravenous (i.v.) bolus for 5 days every 3–4 weeks, have indicated a maximum tolerated dose (MTD) of 1.5 mg/m^2/day with myelosuppression, in particular neutropenia, as the dose limiting toxicity (DLT) [9–12]. Non-haematological toxicities were usually mild and reversible. Phase II studies with this regimen given every 21 days showed promising results in patients with small cell lung cancer and in pretreated patients with ovarian cancer [13–19]. Recently, the drug was registered for the latter indication. Other solid tumours appear much less sensitive to this regimen [20–29]. Daily i.v. administration of topotecan is inconvenient to patients, and oral administration would be a more convenient method of drug administration.

Recent studies in humans using oral administration of the i.v. formulation revealed a 32–44% bioavailability of oral topotecan [30, 31]. No relationship was found between bioavailability of topotecan and age, gender, performance score and the presence of liver metastasis [31]. We present a phase I study of oral topotecan once daily $\times 5$ every 3 weeks, a dose schedule comparable to the daily $\times 5$ i.v. administration.

PATIENTS AND METHODS

Patient selection

Patients with a histologically confirmed diagnosis of malignant solid tumour refractory to standard forms of therapy were eligible. Other eligibility criteria included: age ≥ 18 years; WHO performance status ≤ 2; an estimated life expectancy of ≥ 12 weeks; no previous anticancer therapy ≥ 4 weeks (6 weeks for nitrosoureas or mitomycin C); adequate haematopoietic (white blood cell (WBC) $\geq 4\times10^9$/l and platelets $\geq 100\times10^9$/l), hepatic (bilirubin within normal limits, aspartate amino transferase (AST), alanine amine transferase (ALT) and/or alkaline phosphatase $\leq 2\times$ normal), and renal function (serum creatinine ≤ 133 μmol/l (2.0 mg/dl)). Specific exclusion criteria included: active peptic ulcer or any gastrointestinal condition (including prior upper gastrointestinal resection) which could alter absorption or motility; patients taking H_2-antagonists or proton pump inhibitors. All patients gave written informed consent before entry into the study.

Treatment and dose escalation

Based on our previous data [32] using topotecan for 10 days once daily, and given the human bioavailability data [30, 31], the starting dose for the 5-day oral administration was set at 1.2 mg/m^2/day once daily. Courses were to be repeated every 21 days as tolerated. Dose escalations were based on the toxicity seen at the prior dose level. If no toxicity was seen in the prior dose, $\leq 100\%$ dose escalation was permitted. However, if toxicity was seen, a dose escalation of 15% (depending on the type and severity of toxicity seen at the previous dose level) was prescribed. 3 patients were entered at the lowest dose level, and 6–8 patients were accrued on the higher dose levels, to obtain some information on interpatient variability in pharmacokinetics and related toxicity.

The MTD was defined as one dose level below the dose that induced DLT, which were defined as CTC (NCI-Common Toxicity Criteria) grade IV haematological toxicity and/or non-haematological toxicity $\geq$ CTC grade III during the first course in more than 2 of 6 patients. If neutropenia grade IV, thrombocytopenia $\geq$ grade III and/or non-haematological toxicity $\geq$ grade III occurred during treatment days, topotecan administration was stopped immediately. Intrapatient dose escalation was not permitted.

For a patient with an average body surface area of 1.75 m^2, an absolute dose of 4 mg/day could be calculated at the achieved MTD dose level. 6 patients with different body surface areas were studied, including pharmacokinetics, at this fixed dose to determine whether dosing on a mg/m^2/day basis offered any advantage over the easier fixed dose. Topotecan was supplied as capsules containing topotecan HCL, equivalent to either 0.25, 0.50 or 1.00 mg of the anhydrous free base. Capsules had to be stored between 2 and 8°C. Capsules were taken with a glass of water in the morning on an empty stomach with a period of 2 h fasting thereafter. Patients were treated as outpatients.

Treatment assessment

Prior to therapy, a complete medical history was taken and a physical examination was performed. A complete blood count (CBC) including WBC differential, and serum biochemistry involving sodium, potassium, chloride, bicarbonate, calcium, phosphorus, magnesium, creatinine, urea, uric acid, bilirubin, AST, ALT, alkaline phosphatase, total protein and albumin were performed, as were urinalysis, electrocardiogram and chest X-ray. Weekly evaluations included history, physical examination, serum chemistry and toxicity assessment according to the CTC [33]. CBC was determined twice weekly. Tumour measurements were performed after every two courses and evaluated according to the WHO criteria for response [34]. Patients were taken off the protocol in cases of disease progression.

Pharmacokinetics

For pharmacokinetic analysis, whole blood samples (2.8 ml) in heparinised tubes were collected from an indwelling i.v. canula, prior to dosing, 15, 30, 45 min and 1, 1.5, 2.5, 3.5, 4.5, 8.5 and 12 h after administration of the drug on days 1 and 4 of the first course. The samples were processed and analysed according to the method previously described [35]. The lower limit of quantitation (LLQ) was 0.1 ng/ml for topotecan lactone, as well as for the ring-opened hydroxy-acid. The areas under the plasma concentration–time curves ($(AUC)_{o\text{-infinity}}$) of topotecan lactone and hydroxy-acid were calculated by non-compartmental analysis (linear-logarithmic trapezoidal method). The terminal half-life was calculated as $\ln 2/k$, where k is the elimination rate constant (h^{-1}). The AUC was fitted to the observed percentage decrease in WBC using the sigmoidal E_{max} model [36]. For all calculations, the Siphar software package release 4.0 (Siphar SIMED, Cedex, Creteil, France) was used. For statistical analysis, linear regression analysis was employed to evaluate relationships between dose and dose/m^2 and the AUC, and Pearson correlation coefficients were calculated. Spearman rank correlation coefficients were calculated between the AUC and the percentage decrease in leucocytes, granulocytes and platelets.

RESULTS

A total of 29 patients were entered into the study. Patient characteristics are given in Table 1. All patients were eligible and evaluable for toxicity and response. The total number of evaluable courses was 109. The median number of courses given per patient was two (range 1–14).

Table 1. *Patient characteristics*

No. patients entered	29
No. patients evaluable	29
Age (years)	
Median	53
Range	27–72
Sex	
Female	16
Male	13
WHO performance status	
Median	0
Range	0–1
Prior treatment	
Chemotherapy	19
Radio- and chemotherapy	3
No prior therapy	7
Tumour types	
Colorectal	10
Ovarian	3
Hepatocellular	2
Breast	2
Non-small cell lung cancer	2
Small cell lung cancer	2
Miscellaneous	8

The dose levels studied were 1.2, 1.8, 2.3, 2.7 mg/m^2/day and an additional dose level of 4 mg/day fixed dose.

Haematological toxicity

CTC grade III–IV leucopenia and granulocytopenia were observed in 13 (11.9%) and 23 (21.1%) of 109 courses, respectively (Table 2). Myelosuppression was dose limiting at 2.7 mg/m^2/day in 3 of 7 patients, involving both granulocytopenia and thrombocytopenia grade IV. CTC grade III–IV granulocytopenia occurred in all 7 patients at this dose level, 3 patients had concomitant CTC grade III–IV thrombocytopenia. CTC grade IV granulocytopenia was complicated in 1 patient by neutropenic fever lasting 2 days. CTC grade III–IV myelosuppression occurred in four of 15 courses in 4 of 8 patients treated with 2.3 mg/m^2/day, 2 of these patients were heavily pretreated with three prior chemotherapy regimens. The median day of onset of CTC grade III–IV leucopenia was day 12 (range 9–15) with a median duration of 5.5 days (range 3–10). CTC grade III–IV granulocytopenia occurred at a median of 11 days (range 8–15) with a median duration of 6.5 days (range 2–12).

In eight courses (7.3%) CTC grade III–IV thrombocytopenia was observed, seven times in conjunction with CTC grade III–IV granulocytopenia. CTC grade III–IV thrombocytopenia occurred on day 14 (range 10–15) with a median duration of 7 days (range 2–12 days). In view of these side-effects, 2.3 mg/m^2/day topotecan for 5 days was considered to be the MTD.

Treatment delay due to prolonged myelosuppression occurred in 8 patients. One patient treated at the 4 mg/day dose level had treatment delays of 1 week in three of 10 courses, because of CTC grade II granulocytopenia on day 21. In 7 patients, a treatment delay of 1 week occurred after the first course because of slow recovery from CTC grade III–IV granulocytopenia. Anaemia $\geq$ CTC grade II occurred in 37 (33.9%) of 109 courses in 17 patients (58.6%). A total of 54 units of packed cells were given to 14 patients over 27 (24.8%) courses. Platelet transfusions were given in four (3.7%) courses to 4 (13.8%) patients.

In the patients treated with the 4 mg/day fixed dose, no clinically relevant myelosuppression was seen, six courses with uncomplicated CTC grade III granulocytopenia occurred. In 1 patient, a treatment delay of 1 week occurred related to persistent CTC grade II granulocytopenia on day 21 in three of 10 treatment cycles.

Non-haematological toxicity

Non-haematological toxicity was mild. The most frequent of these side-effects are listed in Table 3. CTC grade III nausea and CTC grade III–IV vomiting were observed in five (4.6%) and four (3.7%) of all courses, respectively. Mild nausea and vomiting could be circumvented with standard anti-emetics (peripheral dopamine antagonists).

Mild anorexia and mild fatigue were reported in 8 (27.6%) and 14 (48.3%) patients, moderate anorexia and fatigue occurred in 2 (6.9%) and 3 (10.3%) patients, respectively. Fatigue was experienced during topotecan intake or in the first week thereafter and subsided within a few days. In 1 patient (dose level 2.7 mg/m^2/day), fatigue was the reason for a 1 week delay of the next course. CTC grade II alopecia occurred in 4 patients at the higher dose levels. Diarrhoea $\geq$ CTC grade II was seen in 6 patients (20.7%) at all dose levels except 1.2 mg/m^2/day. 5 patients had CTC grade II diarrhoea which was self limiting and lasted between 1 and 6 days. One patient, who had disease progression of a peritoneal carcinomatosis of colon cancer, developed CTC grade IV diarrhoea. Other mild non-haematological toxicities reported were: upper abdominal discomfort (10 courses), headache during topotecan intake (two courses) and CTC grade I stomatitis (two courses).

At the 4 mg/day fixed dose level studied, 5 patients experienced only mild nausea, vomiting and mild fatigue, 1 patient CTC grade II diarrhoea, and 1 patient CTC grade II

Table 2. *Haematological toxicities (CTC grades; worst per course)*

			Leucocytes		Granulocytes		Platelets	
Dose level (mg/m^2)	No. of patients	No. of courses	III	IV	III	IV	III	IV
1.2	4(1)*	19	0	0	0	0	0	0
1.8	10(5)*	31	2	0	4	1	2	1
2.3	8	15	2	3	1	3	0	2
2.7	7	10	5	1	4	4	1	2
4 mg flat	6	34	0	0	6	0	0	0
Total	29	109						

*The number in parentheses is the number of patients also studied at this dose level but previously treated at a higher dose level.
CTC, NCI-Common Toxicity Criteria.

Table 3. Non-haematological toxicities (CTC grades; worst per course)

Dose level (mg/m^2)	No. of courses	Nausea			Vomiting				Diarrhoea				Fatigue		Anorexia		Abdominal discomfort
		I	II	III	I	II	III	IV	I	II	III	IV	I	II	I	II	
1.2	19	3	0	1	4	0	0	1	1	0	0	0	4	0	1	1	0
1.8	31	17	0	1	6	0	1	0	2	1	0	0	5	2	1	0	0
2.3	15	6	1	2	5	1	0	2*	1	2	0	0	6	0	3	1	4
2.7	10	6	1	1	5	2	0	0	3	1	0	1*	3	3	4	0	3
4 mg flat	34	23	0	0	10	2	0	0	2	3	0	0	7	0	1	0	3
Total	109																

*Relationship to topotecan possible. CTC, NCI-common toxicity criteria.

Table 4. Pharmacokinetics of oral topotecan once daily ×5 (median ± standard deviation)

Dose level (mg/m^2)	Dose (mg)	Topotecan lactone (day 1) AUC (t) (ng.h/ml)	$t_{1/2}$ (h)	Hydroxy-acid (day 1) AUC (t) (ng.h/ml)	$t_{1/2}$ (h)	Topotecan lactone (day 4) AUC (t) (ng.h/ml)	$t_{1/2}$ (h)	Hydroxy-acid (day 4) AUC (t) (ng.h/ml)	$t_{1/2}$ (h)
1.20 ($n=3$)	2.25	16.65	4.22	34.83	3.99	15.46	2.17	27.17	3.65
	(0.14)	(4.58)	(1.17)	(6.28)	(2.43)	(4.31)	(1.57)	(11.20)	(0.63)
1.80 ($n=3$)	3.00	19.39	2.07	37.75	2.62	21.92	2.91	46.05	3.35
	(0.38)	(3.57)	(1.19)	(8.07)	(1.23)	(2.99)	(0.12)	(11.17)	(0.19)
2.30 ($n=6$)	3.95	20.93	3.80	35.51	3.23	28.70	3.58	39.46	4.23
	(0.25)	(7.15)	(1.09)	(11.04)	(0.64)	(10.87)	(1.36)	(20.29)	(1.27)
2.70 ($n=4$)	5.20	37.01	2.73	62.36	2.70	47.44	4.03	79.81	4.31
	(0.45)	(13.90)	(0.60)	(26.70)	(1.11)	(11.90)	(0.46)	(41.31)	(0.34)
4 mg flat ($n=6$)	4.00	23.80	3.24	46.60	4.00	25.19	4.51	43.33	3.87
		(8.81)	(2.78)	(14.95)	(0.50)	(6.65)	(2.37)	(10.20)	(0.88)

$t_{1/2}$, half-life; AUC, total area under the curve.

alopecia. Skin rash, haematuria, liver or renal toxicity were not observed with topotecan administration.

Pharmacokinetics and dynamics

Pharmacokinetics were performed in 22 patients (Table 4). The AUC of topotecan lactone and hydroxy-acid showed substantial variation. The mean AUC of topotecan lactone for all patients on day 4 (27.7 ± 11.8 ng.h/ml) is similar to the AUC on day 1 (23.4 ± 9.7 ng.h/ml) (non-significant). The interpatient % coefficient of variation (%CV) in the AUC of topotecan lactone on day 1 was 41.5% and the intrapatient variation was 18.5%. There was a low but significant correlation between dose level and the AUC of topotecan lactone day 1 ($R=0.59$, $P=0.02$). The correlation coefficient was $R=0.52$ ($P=0.04$) between the absolute dose of topotecan and the AUC of topotecan lactone.

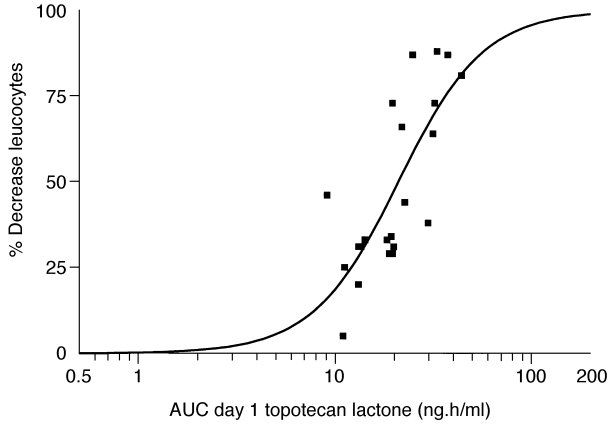

Figure 1. Sigmoidal relationship between the area under the curve (AUC) of topotecan and the percentage decrease in leucocytes.

The correlation between the AUC of topotecan lactone and the percentage decrease in granulocytes and platelets was significant with $R=0.85$ ($P<0.01$) and $R=0.66$ ($P<0.01$), respectively. A sigmoidal relationship (gamma of the slope: 3.06) was found between the AUC day 1 and the percentage decrease in leucocytes (Figure 1; $R=0.76$, $P<0.01$). Finally, the fixed dose of 4 mg/day topotecan for 5 days was studied in 3 female and 3 male patients of different height and weight and, thus, different body surface area. Pharmacokinetic analysis of the 4 mg/day dose level revealed similar AUC and half-life as compared with the dose of 2.3 mg/m^2/day (non-significant) (Table 4). At the 4 mg/day dose level, the mean AUC of topotecan lactone was 22.8 ± 8.8 ng.h/ml and 23.0 ± 7.1 at the 2.3 mg/m^2/day dose level.

Responses

A minor response (40% tumour reduction) was seen in 1 patient with liver metastasis of gall bladder cancer lasting for 30 weeks. Stable disease was noted in 5 patients for a median duration of 30 weeks (range 18–52 weeks).

DISCUSSION

Administration of i.v. topotecan daily for 5 days every 3 weeks has short-lasting non-cumulative neutropenia and/or thrombocytopenia as the DLT [9–12]. The daily ×5 i.v.

administration of topotecan has shown antitumour activity in a variety of malignancies, such as ovarian cancer and small cell lung cancer, and was recently registered in Europe and the U.S.A. for the second-line treatment of patients with ovarian cancer [13–19].

A bioavailability of 32–44% of oral topotecan with moderate intrapatient variation creates the opportunity to study different dose schedules for oral administration.

In the present study, topotecan was adminstered daily for 5 days every 3 weeks, similar to the most frequently studied and recently registered schedule of i.v. administration [13–29]. The DLT with oral topotecan daily $\times 5$ every 3 weeks was myelosuppression which is comparable to the i.v. daily $\times 5$ schedule. The nadirs of leucopenia and granulocytopenia were at days 12 and 11 and lasted 5.5 and 6.5 days, respectively. The day of onset of granulocytopenia is in concordance with previous studies of i.v. topotecan daily $\times 5$ in which the nadir of granulocytes was reported between days 8 and 15. The median duration of granulocytopenia was 6.5 days (range 2–12 days) with orally administered topotecan, the duration was reported to be 3–5 days in the studies with i.v. administration [9–12].

The DLT was reached at 2.7 mg/m^2/day and the MTD was determined as 2.3 mg/m^2/day. At 2.3 mg/m^2/day, ultimately 8 patients were included. In 4 patients, CTC grade III–IV uncomplicated neutropenia occurred. However, 2 of these 4 patients were heavily pretreated with three prior chemotherapy regimens. Since, taken together, only five of 15 courses of this dose level resulted in (uncomplicated) grade IV myelosuppression, we considered the 2.3 mg/m^2/day dose level as the MTD.

Assuming an average body surface area of 1.75 m^2, an average fixed dose of 4 mg/day was calculated at the MTD of 2.3 mg/m^2/day. Although this flat dose was only studied for pharmacokinetic purposes, it is remarkable that myelotoxicity of topotecan seemed limited to uncomplicated granulocytopenia grade III. However, at this dose level, 2 of 6 patients studied had been pretreated with two prior chemotherapy regimens in contrast to 4 of 8 patients treated at the 2.3 mg/m^2/day dose level who were pretreated with $\geq$ two chemotherapy regimens. In other words, patient selection might explain the difference in toxicity; as discussed later, the pharmacokinetics were not dissimilar.

Anaemia $\geq$ CTC grade II occurred in 17 patients (58.6%) in 24.8% of courses. Anaemia is a well documented toxicity occurring in 11–37% of patients in phase I–II studies with i.v. administration of topotecan [13–15, 19, 22]. Similar to daily $\times 5$ i.v. topotecan, non-haematological toxicities with the oral formulation were mild and consisted mostly of nausea and vomiting, which could be easily controlled with conventional anti-emetics. Other non-haematological toxicities consisted of fatigue, anorexia and upper abdominal discomfort. In contrast to the i.v. daily $\times 5$ administration, where diarrhoea, if occurring, is always CTC grade ≤ 1, diarrhoea $\geq$ CTC grade II occurred in 20.7% of patients with oral administration of topotecan. Diarrhoea was mild in the majority of cases and always self limiting.

In a phase I study with oral administration of topotecan twice daily for 21 days every 28 days, the DLT consisted of diarrhoea with a median day of onset of day 15 and a median duration of 8 days (range 7–16) [37]. Prolonged daily oral administration appears to have more intestinal side-effects with more vigorous diarrhoea of longer duration. Diarrhoea $\geq$ CTC grade II has been reported as severe toxicity in patients treated with oral administration of 20-S-camptothecin (40%) and 9-nitro-camptothecin (38%) [38, 39]. In patients treated with i.v. CPT-11 and 20-S-camptothecin, diarrhoea had been reported as severe toxicity [40–42]. In view of the difference between the results from oral and i.v. topotecan, one possibility is that diarrhoea of oral topotecan is due to local effects at the intestinal mucosa. However, the exact mechanism of the cause of the diarrhoea is unknown, but oral exposure to topotecan of limited duration seems feasible and should certainly be considered.

Pharmacokinetic analyses were performed at all dose levels, showing a low but significant correlation between the dose levels and the AUC of the lactone form of topotecan. Pharmacokinetics were studied at a fixed dose of 4 mg/day in order to determine if dosing on a mg/m^2 basis offered any advantage over the easier fixed dose. Pharmacokinetics showed no differences between patients treated with 4 mg/day and patients treated at the 2.3 mg/m^2/day dose level. The AUC and half-life were similar. Non-haematological toxicities observed were comparable. Differences in myelotoxicity with the two dosages compared could be explained from differences in the levels of pretreatment of patients, as stated previously. Significant sigmoidal relationships were established between the AUC of topotecan lactone and the percentage decrease in leucocytes, granulocytes and platelets. Compared with the daily $\times 5$ i.v. administration, oral topotecan resulted in a lower systemic exposure to the drug.

Since the side-effects are nevertheless similar, an appropriate explanation for the difference is lacking. However, since oral topotecan showed significant myelotoxicity, systemic exposure from oral administration may be sufficient to induce antitumour effects. 6 patients in our study with stable disease were treated for six to 14 courses with topotecan, no cumulative haematological or non-haematological toxicity occurred.

In conclusion, orally administered topotecan given daily for 5 days every 3 weeks has myelosuppression as the DLT. The recommended dose for phase II studies is 2.3 mg/m^2/day, or alternatively a fixed dose of 4 mg/day. Further studies are needed to explore fully the potential of oral topotecan as an antitumour agent. Studies comparing daily $\times 5$ i.v. to daily $\times 5$ oral, as well as a phase I study of oral topotecan combined with i.v. cisplatinum, are ongoing.

1. Kingsburry WD, Boehm JC, Jakas DR, *et al.* Synthesis of water soluble (aminoalkyl) camptothecin analogues: inhibition of topoisomerase I and antitumor activity. *J Med Chem* 1991, **34**, 98–107.
2. Champoux J. Evidence from an intermediate with a single strand break in the reaction catalyzed by the DNA un-twisting enzyme. *Proc Natl Acad Sci USA* 1976, **73**, 3488–3491.
3. Camilloni G, Di Martino E, Caserta M, *et al.* Eukaryotic DNA topoisomerase I is topology dependent. *Nucleic Acids Res* 1988, **16**, 7071–7085.
4. Camilloni G, Di Martino E, Di Mauro E, *et al.* Regulation of the function of eukaryotic DNA topoisomerase I: topological conditions for inactivity. *Proc Natl Acad Sci USA* 1989, **86**, 3080–3084.
5. Muller M. Quantitation of eukaryotic topoisomerase I reactivity with DNA. Preferential cleavage of supercoiled DNA. *Biochem Biophys Acta* 1985, **824**, 263–267.
6. Muller M, Pfund W, Metha V, *et al.* Eukaryotic type I isomerase is enriched in the nucleolus and catalytically active on ribosomal DNA. *EMBO J* 1985, **4**, 1237–1243.

7. Hsiang YH, Hertzberg R, Hecht S, *et al.* Camptothecin induces protein-linked DNA breaks via mammalian DNA topoisomerase I. *J Biol Chem* 1985, **260**, 14873–14878.
8. Hsiang YH, Liu LF. Identification of mammalian DNA topoisomerase I as an intracellular target of the anticancer drug camptothecin. *Cancer Res* 1988, **48**, 1722–1726.
9. Rowinsky EK, Grochow LB, Hendricks CB, *et al.* Phase I and pharmacologic study of topotecan: a novel topoisomerase I inhibitor. *J Clin Oncol* 1992, **10**, 647–656.
10. Van Warmerdam LJC, Verweij J, Schellens JHM, *et al.* Pharmacokinetics and pharmacodynamics of topotecan administered in a daily times five regimen every three weeks. *Cancer Chemother Pharmacol* 1995, **35**, 237–245.
11. Verweij J, Lund B, Beijnen JH, *et al.* Phase I and pharmacokinetic study of topotecan, a new topoisomerase I inhibitor. *Ann Oncol* 1993, **4**, 673–678.
12. Saltz L, Sirott M, Young C, *et al.* Phase I clinical and pharmacology study of topotecan given daily for 5 consecutive days to patients with advanced solid tumors, with attempt at dose intensification using recombinant granulocyte colony-stimulating factor. *J Natl Cancer Inst* 1993, **85**, 1499–1507.
13. Schiller JH, Kim K, Johnson D. Phase II study of topotecan in extensive stage small cell lung cancer. *Proc Am Soc Clin Oncol* 1994, **13**, 330 (Abstract 1093).
14. Wanders J, Ardizanni A, Hansen HH, *et al.* Phase II study of topotecan in refractory and sensitive small cell lung cancer (SCLC). *Proc Am Assoc Cancer Res* 1995, **36**, 237 (Abstract 1415).
15. Kudelka A, Edwards C, Freedman R, *et al.* An open phase II study to evaluate the efficacy and toxicity of topotecan administered intravenously as 5 daily infusions every 21 days to women with advanced epithelial ovarian carcinoma. *Proc Am Soc Clin Oncol* 1993, **12**, 259 (Abstract 821).
16. Armstrong D, Rowinsky E, Donehower R, *et al.* A phase II trial of topotecan as salvage therapy in epithelial ovarian cancer. *Proc Am Soc Clin Oncol* 1995 **14**, 275 (Abstract 769).
17. Creemers GJ, Bolis G, Gore M, *et al.* Topotecan, an active drug in the second line treatment of epithelial ovarian cancer: results of a large European phase II study. *J Clin Oncol* 1996, **14**, 3056–3061.
18. Carmichael J, Gordon A, Malfetano J, *et al.* Topotecan, a new active drug vs paclitaxel in advanced epithelial ovarian carcinoma: international topotecan study group trial. *Proc Am Soc Clin Oncol* 1996, **15**, 283 (Abstract 765).
19. Malmstrom H, Sorbe B, Simonsen E. The effect of topotecan in platinum refractory ovarian cancer. *Proc Am Soc Clin Oncol* 1996, **15**, 299.
20. Lynch TJ, Kalish L, Strauss G, *et al.* Phase II study of topotecan in metastatic non-small cell lung cancer. *J Clin Oncol* 1994, **12**, 347–352, 1994.
21. Perez-Soler R, Fossella FV, Glisson BS, *et al.* Phase II study of topotecan in patients with advanced non-small cell lung cancer (NSCLC) previously untreated with chemotherapy. *J Clin Oncol* 1996, **14**, 503–513.
22. Sugarman SM, Agani JA, Daugherty K, *et al.* A phase II trial of topotecan (TPT) for the treatment of advanced measurable colorectal cancer. *Proc Am Soc Clin Oncol* 1994, **13**, 225 (Abstract 686).
23. Kraut EH, Stanbus A, Mayernich D, *et al.* Phase II trial of topotecan in metastatic malignant melanoma. *Proc Am Assoc Cancer Res* 1995, **36**, 238 (Abstract 1420).
24. Robert F, Wheeler RH, Molthrop DC, *et al.* Phase II study of topotecan in advanced head and neck cancer: identification of a new active agent. *Proc Am Soc Clin Oncol* 1994, **13**, 281 (Abstract 905).
25. Smith RE, Lew D, Rodriguez GI, *et al.* Evaluation of topotecan in recurrent or metastatic head and neck cancer. *Proc Am Soc Clin Oncol* 1996, **15**, 310, (Abstract 868).
26. Ilson D, Motzer RJ, O'Moore P, *et al.* A phase II trial of topotecan in advanced renal cell carcinoma. *Proc Am Soc Clin Oncol* 1993, **12**, 248 (Abstract 779).
27. Giantonio BJ, Kosierowski R, Ramsey HE. Phase II study of topotecan for hormone refractory prostate cancer (HRPC). *Proc Am Soc Clin Oncol* 1993, **12**, 247 (Abstract 774).
28. Noda K, Sasaki H, Yamamoto K, *et al.* Phase II trial of topotecan for cervical cancer of the uterus. *Proc Am Soc Clin Oncol* 1996, **15**, 280 (Abstract 754).
29. Puc HS, Bajorin DF, Bosl GJ, *et al.* Phase II trial of topotecan in patients with cisplatin-refractory germ cell tumors. *Investig New Drugs* 1995, **13**, 163–165.
30. Kuhn J, Rizzo J, Eckardt J, *et al.* Phase I bioavailability study of oral topotecan. *Proc Am Soc Clin Oncol* 1995, **14**, 474 (Abstract 1538).
31. Schellens JHM, Creemers GJ, Beynen JH, *et al.* Bioavailability and pharmacokinetics of oral topotecan: a new topoisomerase I inhibitor. *Br J Cancer* 1996, **73**, 1268–1271.
32. Burris H, Gerrits CM, Schellens JHM, *et al.* Oral topotecan for 10 days once daily and twice daily every 3 weeks: a phase I and pharmacologic study in adults. *Ann Oncol* 1996, **7**, 126 (Suppl. 5).
33. National Cancer Institute. *Guidelines for Reporting of Adverse Drug Reactions*. Bethesda, Division of Cancer Treatment, National Cancer Institute, 1988.
34. World Health Organisation. *WHO Handbook for Reporting Results of Cancer Treatment*. WHO offset publication No 40. Geneva, Switzerland, World Health Organisation, 1979.
35. Loos WJ, Stoter G, Verweij J, *et al.* Sensitive high-performance liquid chromatographic fluorescence assay for the quantitation of topotecan (SKF 104864-A) and the lactone ring-opened product (hydroxy-acid) in human plasma and urine. *J Chromatography B* 1996, **678**, 309–315.
36. Holford NH, Scheiner LB. Understanding the dose–effect relationship: clinical application of pharmacokinetic–pharmacodynamic models. *Clin Pharmacokinet* 1981, **6**, 242–247.
37. Creemers GJ, Gerrits CJH, Eckardt JR, *et al.* Phase I and pharmacologic study of oral topotecan administered twice daily for 21-days to adult patients with solid tumors. *J Clin Oncol* 1997, **15**, 1087–1093.
38. Stehlin JS, Natelson EA, Hinz HR, *et al.* Phase I clinical trial and pharmacokinetic results with oral administration of 20-S-camptothecin. In Potmesil M, Pinedo H, eds. *Camptothecins: New Anticancer Agents*. Boca Raton, CRC Press, 1995, 59–65.
39. Verschraegen CF, Natelson E, Giovanella B, *et al.* Phase I study of oral 9-nitro-camptothecin (9NC). *Proc Am Soc Clin Oncol* 1996, **15**, 482 (Abstract 1532).
40. Fukuoka M, Noriyuki M. Clinical studies of irinotecan alone or in combination with cisplatin. *Cancer Chemother Pharmacol* 1994, **34**, S105–S111.
41. Schlichenmyer WJ, Rowinsky EK, Donehower RC, *et al.* The current status of camptothecin analogues as antitumor agents. *J Natl Cancer Inst* 1993, **85**, 271–291.
42. Creemers GJ, Lund B, Verweij JJ. Topoisomerase I inhibitors: topotecan and irinotecan. *Cancer Treatment Rev* 1994, **20**, 73–96.